RESEARCH ARTICLE

Low Level of Consanguinity in Moroccan Families at High Risk of Breast Cancer

Siham Chafai Elalaoui[1,2]*, Imane Cherkaoui Jaouad[1,2], Fatima Zahra Laarabi[1,2], Brahim El Khalil Elgueddari[3], Noureddine Benjaafar[3], Abdelaziz Sefiani[1,2]

Abstract

Background: Breast cancer is worldwide the most common cancer in women and is a major public health problem. Genes with high or low penetrance are now clearly implicated in the onset of breast cancer, mostly the BRCA genes. All women in families at high risk of breast cancer do not develop tumours, even when they carry the familial mutation, suggesting the existence of genetic and environmental protective factors. Several studies have shown that consanguinity is linked to a decreased or an increased risk of breast cancer, but to the best of our knowledge, there is no study concerning the association between consanguinity and the occurrence of tumours in women with high risk of breast cancer. The objective of this study was to examine whether parental consanguinity in families with genetic predisposition to breast cancer affect the risk of siblings for having this cancer. Materials and Methods: Over a six-year period, 72 different patients with a histological diagnosis of breast or ovarian cancer from 42 families were recruited for genetic counselling to the Department of Medical Genetics, Rabat. Consanguinity rate was determined in cases and compared to the consanguinity rate in the Moroccan general population. Results: Consanguinity rates were 9.72% in patients and 15.3% in controls, but the difference was statistically not significant (p>0.001) and the mean coefficient of consanguinity was lower in breast cancer patients (0.0034) than in controls (0.0065). Conclusions: Despite the relatively small sample size of the current study, our results suggest that parental consanguinity in Moroccan women might not be associated with an altered risk of breast cancer. Large scale studies should be carried out to confirm our results and to develop public health programs.

Keywords: Breast cancer - consanguinity - Moroccan population

Asian Pacific J Cancer Prev, **14 (2)**, 723-726

Introduction

Breast cancer is the most common malignancy affecting women worldwide (Boyley et al., 2005). 5-10% of all breast cancer cases that show strong familial history are caused by inherited mutations in many genes mainly BRCA1 and BRCA2 (Rowell et al., 1994; Antoniou et al., 2003).

The development of cancer in women from families at high risk is probably more related to genetic than environmental factors, and a possible relationship between consanguinity and cancer should be examined. Different types of consanguineous marriages impart in offspring a different probability of homozygosity by descent. The probability of homozygosity decreases exponentially from a more closely inbred to a less inbred offspring. In fact, consanguinity which increases the chances of homozygosity, was linked to an increased risk of breast cancer by many authors (Simpson et al., 1981; Shami et al., 1991; Rudan et al., 1999; Liede et al., 2002; Denic et al., 2003; Denic et al., 2007). However, studies conducted in other populations have shown that consanguinity does not affect, or may be protective for breast cancer risk (Denic et al., 2001; Denix et al., 2005; Bener et al., 2010). This suggests that the effect of inbreeding on cancer risk may differ for different tumours, for the same tumour and may vary between populations. Genes with protective effect exhibit incomplete penetrance and the age at diagnosis of breast and/or ovarian cancer varies remarkably among mutation carriers (Antoniou et al., 2003).

In spite of a large consanguineous population in Africa and Arab Countries, the effect of inbreeding on developing breast cancer in these countries is still unclear. In this study, we examined the parental consanguinity level and the possible effect of inbreeding on the risk of breast cancer in Moroccan families at high risk.

*[1]Centre de génomique humaine, Faculté de Médecine et de Pharmacie, Université Mohammed V Souissi, [2]Département de Génétique Médicale, Institut National d'Hygiène, [3]Service de Radiothérapie, Institut National d'Oncologie, Rabat, Morocco *For correspondence: sihamgen@yahoo.fr*

Materials and Methods

From 2004-2010, seventy two breast cancer patients were referred for genetic counselling to the Department of Medical Genetics (Institut National d'Hygiène, Rabat). All patients were Moroccan women with confirmed breast or ovarian cancer and histological diagnosis of tumours. Only women with young age of cancer onset (<30 years) or with familial strong history of breast cancer were enrolled in the study. Consanguinity was determined for 72 different siblings from 42 families.

The genealogical data were obtained from patients files. Consanguineous marriages were classified into first cousins (including parallel paternal, parallel maternal, cross and double first cousins) and beyond first cousins (including first cousins once removed and second cousins). Other couples were related with a distant consanguinity, and those reported as from the same tribe were considered non-consanguineous. Consanguinity was evaluated based upon the coefficient of inbreeding (F) which is the probability of homozygosity by descent and was determined in the offspring of six types of consanguineous union. Moreover, the consanguinity profile was compared for the breast cancer women with the consanguinity profile of the general population (Jaouad et al., 2009).

Data were analysed using Statistical methods. The Mantel-Haenzel χ^2 test was utilized to establish the association between our variables and calculate the odds ratio (OR) and 95% confidence intervals (CI). P-values which are less than 0.001 were considered statistically significant.

Results

Of the 72 patients with a breast or ovarian cancer, 7 were found to be consanguineous, giving an overall rate of consanguinity of 9.72% (CI: 2.9; 16.5). The mean coefficient of consanguinity was lower in breast cancer patients (0.0034) than in controls (0.0065). The most common type of consanguineous marriage was between first cousins with 57.14% of the total consanguineous marriages and 5.55% of all marriages. Distant consanguinity was common (42.86% of all marriages). The Odds ratio was 0.59 [CI: (0.27;1.2)], but the difference between the two groups was statistically not significant (p>0.001).

Discussion

Consanguineous marriage is traditionally common throughout many countries, especially in the Arab world and Africa (Khlat et al., 1997). The consanguineous marriages result more from cultural and financial reasons rather than religious ones. The consanguineous couples have an increased frequency of abortions, stillbirths, postnatal mortality and children with congenital malformation and autosomal recessive disorders (Grant et al., 1997; Jaber et al., 1998; Jaouad et al., 2009). If a recessive tumour gene is present in a consanguineous child, theoretically, he could be born with two recessive tumour genes, and then has a congenital step of carcinogenesis. Consequently, this individual would be expected to develop cancer earlier in life. However, if a gene causing lethal illness develops before an individual could reproduce; such a deleterious gene would be lost from a population (Khlat et al., 1997). Thus, the practice of consanguinity, as showed for populations in India and the Middle East, will decrease the frequency of those alleles that increase the chances of deaths among younger individuals before they reach reproductive age (Denic et al., 2002). The finding that parental consanguinity reduces the risk of breast cancer should be confirmed, as it may be important for consanguineous families worldwide.

For countries such as Morocco, where consanguinity is common, it seems important to analyse the association between consanguinity and predisposition to breast cancer. To the best of our knowledge, no study has been conducted in Morocco to examine whether parental consanguinity affects the overall risk of breast cancer. The rate of consanguinity (15.25%) is relatively high in Morocco compared to other countries. The most common type of consanguineous marriage was between first cousins, with 58.46% of the total consanguineous marriages. Other studies assessed the consanguinity prevalence in Morocco to be in the range of 19.81-28%, but these studies were related to one region and reflect only the activity of a specific Medical Center (Jaouad et al., 2009).

The present study showed that the rate of parental consanguinity was lower in breast cancer patients (9.72%) than in Controls (15.25%), with an Odds ratio of 0.59 [CI: (0.27;1.2)]. These results indicate that consanguinity might be a protective factor against breast cancer in families at high risk. However, the difference between the two groups is not statistically significant (p>0.001), suggesting that inbreeding may have a small protective effect against breast cancer that could have been detected with a larger study sample. This finding is similar to the result of previous population-based studies conducted in women with breast cancer (Denic et al., 2001; 2005; Bener et al., 2010) showing that the parental consanguinity was more frequent in women without breast cancer than in those with cancer, and that the coefficient of inbreeding was lower in breast cancer patients.

However, in Pakistan, a higher risk of breast cancer was observed in consanguineous women as compared to control population (Gilani et al., 2004; Assie et al., 2008). In five Adriatic islands of Croatia, an increased level of inbreeding was also associated with increased rates of breast and other cancers in predominantly younger populations when compared with the mainland population (Rudan et al., 1999). Familial cases of breast and/or ovarian cancer are due mainly to inherited mutations of BRCA1 and BRCA2 genes. Among 42 unrelated families referred to our Department for genetic testing of BRCA1/2 genes, three different BRCA mutations were identified in 5 families. The BRCA1-185delAG mutation was identified in two families, the mutation BRCA1-c.798_799delTT was found in two families, and the mutation BRCA2 -c.5073dupA in one family (Laarabi et al., 2011).

In consanguineous family, an offspring is more likely to be BRCA1/2 homozygous. The consequences of BRCA1/2 mutation homozygosity in humans are

unknown; the well-known consequence of BRCA2 mutation homozygosity is Fanconi syndrome. On the other hand, the BRCA1 and BRCA2 knock-out mice are not viable and are aborted during embryonic life suggesting that the same situation may cause abortion or stillbirths in humans (Hakem et al., 1998). Probably, the same thing occurs in humans, but because of the scarcity of the event of being homozygote for BRCA1/2, it has not been reported so far. Among the conceptsuses of consanguineous couples, there are abortions, stillbirths, perinatal and early-childhood deaths. Excess deaths may be due to BRCA1/2 and other still undiscovered homozygote tumour genes (Denic et al., 2002). Some of these lost individuals are actually 'lost breast cancer patients'. This suggests that BRCA1/2, causing more breast cancers in younger than older women, are infrequent in populations with a high rate of consanguinity (Denic et al., 2001).

The protective effect of consanguinity in women with high risk of breast cancer may probably be explained by the existence of biallelic DNA variants in these consanguineous persons. Latif et al confirm that susceptibility variants in FGFR2, TOX3 and MAP3K1 are all associated with increased risk of cancer in individuals with a family history of breast cancer, whereas CASP8 is protective (Latif et al., 2010). Individuals with strong family history of breast cancer, without BRCA1 or BRCA2 mutations have a protective effect of the CASP8 variant (Asp302His). This significant association between CASP8 variant and protective effect in negative mutation familial breast cancer cohort was also found in the BRCA1/2 mutation positive cohort (Latif et al., 2010). The CASP8 D302H polymorphism was highly associated with the absence of cancer.

Zhang et al reported in a meta-analysis, different genetic variants associated with breast-cancer risk; 51 variants in 40 genes showed significant associations with breast-cancer risk (Zhang et al., 2011). This association was strong for ten variants in six genes (ATM, CASP8, CHEK2, CTLA4, NBN, and TP53), and moderate for four variants in four genes (ATM, CYP19A1, TERT, and XRCC3). These studies were carried out mainly in Caucasian and Asian populations. Few studies were reported in Arab and African populations. A recent study in an ethnic Arab population (from Saudi Arabia) showed a significant association between the MDM2 309T>G and TP53 72Arg>Pro polymorphisms and the risk of developing breast cancer (Alashtawi et al., 2011).

The effects of inbreeding on the risk of cancer in ethnically different populations require more investigations in consanguineous families worldwide. Furthermore, our findings need to be confirmed by other studies in different populations to explain the protective effect of consanguinity on familial cancer by a probable existence of biallelic DNA variants in these consanguineous individuals.

Acknowledgements

We are grateful to the patients and their families for their cooperation. We thank Professor Rachid Tazi-Ahnini for re-reading the manuscript.

References

Alshatwi AA, Hasan TN, Shafi G, et al (2011). A single-nucleotide polymorphism in the TP53 and MDM-2 gene modifies breast cancer risk in an ethnic Arab population. *Fundam Clin Pharmacol*, **26**, 438-43.

Antoniou AC, Easton DF (2003). Polygenic inheritance of breast cancer: implications for design of association studies. *Genet Epidemiol*, **25**, 190-202.

Antoniou A, Pharoah PD, Narod S, et al (2003). Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet*, **72**, 1117-30.

Assie G, LaFramboise T, Platzer P, et al (2008). Frequency of germline genomic homozygosity associated with cancer cases. *JAMA*, **299**, 1437-45.

Bener A, El Ayoubi HR, Ali AI, et al (2010). Does consanguinity lead to decreased incidence of breast cancer? *Cancer Epidemiology*, **34**, 413-8.

Boyley P, Ferlay J (2005). Cancer incidence and mortality in Europe. *Ann Oncol*, **16**, 481-8.

Denic S, Bener A (2001). Consanguinity decreases risk of breast cancer –cervical cancer unaffected. *Bri J Cancer*, **85**, 1675-9.

Denic S, Al-Gazali L (2002). Breast cancer, consanguinity, and lethal tumor genes: simulation of BRCA1/2 prevalence over 40 generations. *Int J Mol Med*, **10**, 713-9.

Denic S, Al-Gazali L (2003). BRCA1 and BRCA2 mutations in breast cancer patients from Saudi Arabia. *Saudi Med J*, **24**, 696.

Denic S, Bener A, Sabri S, et al (2005). Parental consanguinity and risk of breast cancer: a population-based case-control study. *Med Sci Monit*, **11**, 415-9.

Denic S, Frampton C, Nicholls MG (2007). Risk of cancer in an inbred population. *Cancer Detect Prev*, **31**, 263-9.

Gilani G, Kamal S (2004). Risk factors for breast cancer in Pakistani women aged less than 45 years. *Ann Hum Biol*, **31**, 398-407.

Grant JC, Bittles AH (1997). The comparative role of consanguinity in infant and childhood mortality in Pakistan. *Ann Hum Genet*, **61**, 143-9.

Hakem R, De la pompa JL, Mak TW (1998). Developmental studies of BRCA1 and BRCA2 knock out mice. *J Mammary Gland Biol Neoplasia*, **3**, 431-45.

Jaber L, Halpern GJ, Shohat M (1998). The impact of consanguinity worldwide. *Commun Genet*, **1**, 12-7.

Jaouad IC, Elalaoui SC, Sbiti A, et al (2009). Consanguineous marriages in morocco and the consequence for the incidence of autosomal recessive disorders. *J Biosoc Sci*, **41**, 575-81.

Khlat M (1997). Endogamy in the Arab world. In genetic disorders among Arab populations. AS. Teebi and TI. Farag, eds. New York, 1997:63-80.

Laarabi FZ, Jaouad IC, Ouldim K, et al (2011). Genetic testing and first presymptomatic diagnosis in Moroccan families at high risk of breast/ovarian cancer. *Oncol Lett*, **2**, 389-93.

Latif A, Hadfield KD, Roberts SA, et al (2010). Breast cancer susceptibility variants alter risks in familial disease. *J Med Genet*, **47**, 126-31.

Liede A, Malik IA, Aziz Z, et al (2002). Contribution of BRCA1and BRCA2 mutations to breast and ovarian cancer in Pakistan. *Am J Hum Genet*, **71**, 595-606.

Rowell S, Newman B, Boyd J, et al (1994). Inherited predisposition to breast and ovarian cancer. *Am J Hum Genet*, **55**, 861-5.

Rudan I (1999). Inbreeding and cancer incidence in human isolates. *Hum Biol*, **71**, 173-87.

Shami SA, Qaisar R, Bittles AH (1991). Consanguinity and adult

morbidity in Pakistan. *Lancet,* **338**, 954-5.
Simpson JL, Martin AO, Elias S, et al (1981). Cancers of the breast and female genital system: search for recessive genetic factors through analysis of human isolate. *Am J Obstet Gynecol*, **141**, 629-36.
Zhang B, Beeghly-Fadiel A, Long J, et al (2011). Genetic variants associated with breast-cancer risk: comprehensive research synopsis, meta-analysis, and epidemiological evidence. *Lancet Oncol*, **12**, 477-88.